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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,552	09/22/2003	Johannes Bartholomaeus	029310.50777CP	6176

23911 7590 11/13/2008

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EXAMINER	
TRAN, SUSAN T	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
11/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/665,552	BARTHOLOMAEUS ET AL.	
	Examiner	Art Unit	
	S. Tran	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an oral dosage form of tramadol and diclofenac, does not reasonably provide enablement for the specific release profiles recited in claims 27 and 28. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: breadth of the claims, nature of the invention, state of the prior art, amount of direction provided by the inventor, the level of predictability in the art, the existence of working examples, quantity of experimentation needed to make or use the invention based on the content of the disclosure, and relative skill in the art. All of the factors have been considered with regard to the claim, with the most relevant factors being discussed below:

Breadth of the claims is broad. Independent claim 1 is directed to an oral formulation comprising combination of tramadol and diclofenac in separate subunits. Dependent claims 27 and 28 require specific release profiles from the dosage form of claim 1.

Amount of direction provided by the inventor, and quantity of experimentation needed to make or use the invention: independent claim 1 does not recite any structure of the dosage form that specifically leads to the claimed release profiles. Much less, the claims broadly recite just an oral dosage form. There are quite a large number of dosage forms out there that are suitable for oral administration. A review of the present specification shows that different dosage forms with different structures result in different release profiles (see examples 1-4). Further, the present specification does not teach how to precisely achieve the claimed release patterns or profiles given the multitudes of types of suitable dosage forms with multitudes types of coating polymers. The specification also fails to teach if different release profiles can be achieved from the same dosage form as recited in claim 1. The specification does not provide any guidance as to how one can achieve different types of release rates with the same amount of drug in a dosage form. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap. As such, the practitioner would turn to trial and error experimentation in order to compose the claimed oral release dosage form of tramadol and diclofenac without guidance from the specification or the prior art.

The relative skill of those in the art: the skill of one of ordinary skill in the art is very high, e.g., Ph.D. and M.D. level technology.

Claim Rejections - 35 USC § 103

Claims 1-9, 11-16, 20, 21, 24 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Voss et al. US 4,690,927, in view of On US 6,319,514.

Voss teaches a pharmaceutical dosage form comprising mixture of diclofenac sodium and salt of codeine in a weight ratio of about 1:1 to 3:1 (abstract; and claims 1-3). The dosage is suitable for oral administration in the form of granule, dragee, tablet, layered tablet, and capsule (column 2, lines 11-64). The two active substances can be formulated in separate layers in a tablet, or as granules incorporated into a capsule (ID). The final dosage form can be film coated with hydroxypropylmethyl cellulose (example 1).

Voss is only deficient in the sense that Voss teaches codeine instead of tramadol as a narcotic compound. However, On teaches a narcotic analgesic includes codeine phosphate, tramadol hydrochloride, and related analogues having similar analgesic property (column 3, lines 4-9). Thus, it would have been obvious to one of ordinary skill in the art to, by routine experimentation modify the combination dosage form of Voss to combine diclofenac with tramadol to obtain the claimed invention. This is because On teaches the equivalency or at least similar analgesic property between codeine and tramadol (ID).

Claims 1-9, 11-16, 20, 21, 24 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Voss et al. US 4,690,927, in view of Raffa EP 0 546 676 A1.

Voss is relied upon for the reason stated above. Voss does not expressly teach the use of tramadol as a narcotic compound.

Raffa teaches tramadol and it's salt such as tramadol hydrochloride is an "atypical" opioid analgesic, a very unique drug that when combine with an NSAID, will exhibit superadditive analgesia (page 2, lines 20-21; and page 3, lines 5-7). Thus, it would have been obvious to one of ordinary skill in the art to optimize the combination of Voss to combine diclofenac with tramadol to obtain the claimed invention. This is because Raffa teaches a preferred selection of tramadol over codeine to reduce side effects associated with opioid analgesics (page 2, lines 4-28), and because Voss teaches the desirability of combining diclofenac with an opioid analgesic compound to achieve a more intense therapeutic effect but eliminating side effects (column 2, lines 5-10).

Claims 1-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Voss et al. in view of Raffa or On, and Oshlack et al. US 6,077,533.

Voss is relied upon for the reasons stated above. Voss does not teach the claimed coating materials.

Oshlack teaches a multi-particulate product comprising beads of immediate release active core coated with an extended release coating (abstract; and column 6, lines 8-38). Extended release coating comprises the claimed polymer (column 10, lines 1-67). Extended release coating can be applied as a layer to the immediate release core, or as a controlled release matrix (columns 12-13; and column 14, lines 1-2).

Oshlack further teaches the claimed release profile (column 9, lines 23-46). Active includes tramadol, and nsaid such as diclofenac sodium (column 5, lines 12-25).

Thus, it would have been obvious to one of ordinary skill in the art to modify the dosage form of Voss using the coating composition of Oshlack to obtain the claimed invention. This is because Oshlack teaches a coating composition that is compatible with both diclofenac and tramadol, because Oshlack teaches a coating formulation that is capable of producing a strong, continuous film that is smooth and elegant capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free (column 9, lines 18-22), and this is because Voss teaches the desirability of obtaining a suitable oral dosage form with reduce side-effects.

Response to Arguments

Applicant's arguments filed 08/07/08 have been fully considered but they are not persuasive.

Applicant argues that in the present instance, the scope of the claims is commensurate with the description provided in the specification. The examples provided in the specification represent preferred embodiments which demonstrate the operability of invention to achieve the parameters required by the claims. The skilled artisan has training and experience necessary to tailor pharmaceutical formulations. Based on this training and experience, the skilled artisan could readily practice the full scope of the invention as claimed, without undue experimentation. Because the skilled artisan is highly skilled and has advanced

education and experience and would be able to make and use the claimed invention in its full scope and because the patent laws do not limit the scope of allowable claims to the particular examples in the specification the present claims are adequately supported by the specification and the claims are fully enabled. Reconsideration and withdrawal of this rejection are therefore respectfully requested.

However, in response to applicant's argument, it is noted that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). From the broadest limitation of the present claim 1, the claim does not define any structure of the "oral administration unit" in the sense that would enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Let alone, the present specification discloses quite a number of dosage form that could be selected as an oral administration unit, such as microtablets, microcapules, ion-exchange resinates, granules, crystals or pellets. The unit can be coated with a retard coating comprising multitude type of polymers (paragraphs 0020-0022), such as water-insoluble polymers, water-soluble polymers, and waxes. The unit may further comprise additional coating, and/or matrix materials (paragraphs 0022-0024). With quite a number of different dosage structures, and multitude type of materials that can be incorporated in the dosage unit, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap. This is also evident by the disclosure of the examples in the present specification that, different dosage structure will result in a different

release profile (see examples 1-4). As such, the practitioner would turn to trial and error experimentation in order to compose the claimed oral release dosage form of tramadol and diclofenac without guidance from the specification or the prior art.

Accordingly, the 112, 1st paragraph rejection of claims 27 and 28 are maintained.

Applicant argues that there is nothing in any of the cited art which even hints at the present invention unexpected benefits. For instance, Voss et al. is silent as to any unfavorable physical or chemical interaction between tramadol and codeine. Further, in all of the specific examples provided in Voss et al. the active agents are mixed together, see col. 3, lines 11-12, 41-45 and 55-56. Voss provides no indication that there might be an unfavorable interaction between to active substances when they are provided together. Even comparing the formulation where a core of diclofenac is surrounded by a layer of codeine as described at col. 2, lines 49-52 the benefit of the presently claimed invention is not achieved, because there is no chemical interaction whether between diclofenac and codeine, whether they are mixed together or provided in different layers. Thus, comparing the prior art to the claimed invention, in the prior art, the unexpected and unforeseen benefit of the presently claimed invention is not achieved.

However, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the release of the active ingredients can proceed much faster than if the ingredients were mixed together during the formulation process; an unfavorable

interaction between to active substances when they are provided together) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The present independent claim 1 only requires that the two active substances are present in separate subunits. The present claims, however, do not preclude, for example: 1) mixing the subunits containing the two active substance; and 2) putting them into one unit dosage form. Voss teaches the two active substances can be formulated in separate layers in a tablet, or in separate granules and then incorporating them into a capsule (column 2, lines 46-64).

Further, in response to applicant's argument that *even comparing the formulation where a core of diclofenac is surrounded by a layer of codeine as described at col. 2, lines 49-52 the benefit of the presently claimed invention is not achieved, because there is no chemical interaction whether between diclofenac and codeine, whether they are mixed together or provided in different layers*, it is noted that Voss meets all the limitations require by the present claims, namely, a dosage form having the claimed two active substances in separate subunits. The burden is shifted to applicant to show that the dosage form taught by Voss does not have the benefit of the present invention.

Applicant argues that the On reference is offered in the Office Action as teaching that tramadol may be substituted for codeine. There is no indication that such a substitution would result in a formulation with a delayed release profile. Indeed, the

reality of the chemical interaction between tramadol and diclofenac shows that in fact, tramadol cannot simply be substituted for codeine. The formation of the sparing soluble compound of tramadol (hydrochloride) and diclofenac (sodium) indeed shows that there can be no simple substitution between the various analgesics. As can be seen from Figure 2, if tramadol and diclofenac are embedded together in a conventional matrix tablet, the release profile of both active substances is disadvantageous.

In response to applicant's arguments, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). On is cited solely for the teachings that narcotic analgesic such as codeine phosphate, tramadol hydrochloride, and related analogues having similar analgesic property are well known in the art (column 3, lines 4-9). Thus, one of ordinary skill in the art would have been motivated to, by routine experimentation modify the codeine with tramadol or related analogues having similar analgesic property with the expectation of obtaining a composition similar to that of the claimed invention. This is because On teaches the equivalency or at least similar analgesic property between codeine and tramadol (ID).

Accordingly, the 103(a) rejection over Voss in view of On is maintained.

Applicant argues that the Raffa reference relates to a composition comprising a tramadol material and an NSAID. Raffa does not explicitly disclose the presently claimed combination of tramadol or a pharmaceutically acceptable salt thereof with diclofenac or a pharmaceutically salt thereof. Moreover, Raffa provides no indication that there might be any problem arising from the direct combination of tramadol and diclofenac.

However, in response to applicant's argument, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the present case, Raffa is relied upon solely for the teaching that tramadol is a preferred narcotic analgesic over codeine.

Applicant argues that Oshlack discloses sustained release oral solid dosage forms of opioid analgesics provided as multiparticulate systems containing pharmaceutically acceptable inert beads which are powder layered with therapeutically active agents. Oshlack does not disclose the presently claimed combination of tramadol and diclofenac nor the problem arising from the direct combination of these two active substances. Considering the disclosures of the cited art, there is nothing to teach or suggest that the unexpected benefits afforded by the presently claimed

invention might be achieved. Moreover, it is not clear from the record what would drive the skilled artisan to selectively consider only portions of teachings of the various cited references so as to arrive at the claimed invention. Rather, the proposed combination of these references and the modifications of these references necessary to arrive at the claimed invention is based purely on hindsight, relying on the present claims as a roadmap.

However, in response to applicant's argument, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Oshlack is relied upon solely for the teaching of a coating formulation that is capable of producing a strong, continuous film that is smooth and elegant capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to S. Tran whose telephone number is (571) 272-0606. The examiner can normally be reached on M-F 8:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. Tran/
Primary Examiner, Art Unit 1615